REMARKS

I. PROSECUTION HISTORY

On February 24, 2004, the Office mailed a restriction requirement, and Applicants replied by electing Group II with traverse. With their election, Applicants also filed a preliminary amendment, amending claims, canceling claims 1-18 and adding new claims 31-33. In an Office action mailed June 11, 2004, Groups I and II were rejoined, claims 1-18 and 25-30 were withdrawn from consideration and claims 19-24 and 31-33 were rejected. Applicants thank the Examiner for his assistance in interviews on April 26, 2004 (in which priority claims and structural elements of claims were discussed) and August 18, 2004 (in which claim format, enablement and prior art issues were discussed).

II. AMENDMENTS TO THE CLAIMS

The claims set forth above find support throughout the application as originally filed, as well as support in each priority application, beginning with the Applicants' 1992 application, U.S.S.N. 07/959,951. Exemplary support for the addition of the term "specifically" to claim 20 is found on page 35, lines 7-16. Claims 20 and 24 have been rewritten so as to have a format analogous to claim 33. Claim 33 has been amended to more clearly define the amino acid sequence of fragments with respect to SEQ ID NO: 4. Amendments to the claims are discussed in more detail below (*see, e.g.*, section IV). No new matter is added by this amendment. Applicant reserves the right to pursue, in this or related applications, claims directed to any unclaimed subject matter whether originally claimed, later claimed, or not previously claimed.

III. THE OBJECTION TO THE INFORMATION DISCLOSURE STATEMENT HAS BEEN RENDERED MOOT

The Office objected to 1449 entries C61-C68 of the Information Disclosure Statement (IDS) filed in April 2002 for failure to list publication dates. The supplemental IDS filed concurrently with this response relists entries C61-C68[1] and includes a publication date for each entry. These publication dates were determined by entering the accession number in the EMBL Sequence Version Archive (http://www.ebi.ac.uk/cgi-bin/sva/sva.pl) and using as the publication date, the first database update preceding the date the sequence

[1] "C64" was inadvertently used to refer to two different references in the original IDS. Two "C64s" are again used for sake of consistency. Copies of both C64 references accompany the supplemental IDS.

entry was printed out from the database (the print-out date appears in the lower right-hand corner of each (previously submitted) print-out). In addition to the previously submitted print-outs, Applicants also attach to each print-out a list of the updates for each database entry. Accordingly, the objection has been rendered moot. Applicants respectfully request that the Examiner consider the documents C61-C68, make them of record, and initial the IDS.

IV. THE OBJECTIONS TO CLAIMS 22-24 HAVE BEEN RENDERED MOOT BY THE AMENDMENTS TO THE CLAIMS

The Office objected to claims 22 and 23 for using the language "includes," instead of "comprises." Although "includes" is an accepted term, Applicants have adopted the Office's suggestion and have amended these claims to recite "comprises" because this change does not narrow the claims. "Include" has also been changed to "comprise" elsewhere in the claims, again because this change does not narrow the claims. Claim 24 was objected to for allegedly having broader scope than claim 22 from which it depended. Claim 24 has now been redrafted in independent form. Accordingly, the objections to claims 22-24 have been rendered moot and should be withdrawn.

V. APPLICANTS REQUEST DEFERMENT OF THE DOUBLE PATENTING REJECTION

The Office rejected 19-24 and 31-33 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 38-44 of U.S. Patent No. 5,776,755. Response at this stage is premature because the claims have not yet been deemed allowable but for the alleged double patenting. Applicants plan to submit a terminal disclaimer once one or more claims are allowable but for a maintained double patenting rejection.

VI. THE CLAIMS ARE FULLY ENABLED BY THE SPECIFICATION AS FILED

Beginning on page 5 of the action, the Office rejected claims 19-22, 24, 31, and 33 under 35 U.S.C. § 112, first paragraph, because the specification allegedly did not reasonably enable a Flt4 fragment encoded by 200 nucleotides of SEQ ID NO: 1 or 3, or a polypeptide comprising a Flt4 extracellular domain fragment, or a polypeptide comprising Flt4 peptides obtained by CNBr cleavage. Applicants respectfully traverse.

The Office alleged that the claims covered variants of unpredictable function. This allegation about function is not relevant to the current claims. The claims encompass

polypeptides that comprise Flt4 fragments that are useful for antibody production. The application teaches that Flt4 fragments and other peptides can be made synthetically, using peptidases, or using genetic manipulations. *See, e.g.*, specification at page 32, lines 5-14. The application also teaches how to use the fragments to make antibodies. *See* pages 33-34. The Office does not dispute that this use of the subject matter of the claims have been enabled, and one enabled use is sufficient to enable product claims. The law does not require that additional uses be enabled for product claims, although other uses are taught in the application. Accordingly, the allegation relating to unpredictable receptor function is improper.

The Office alleged that "a fragment sufficient to produce an antibody which binds SEQ ID NOS: 2 or 4" is not a function that the polypeptide performs and that the recited property would have to be confirmed by further testing. *See* page 7 of the action. There is no rule that properties recited in a claim must be a "function that the polypeptide performs." This recited property serves to define a useful invention, and the relevant question is whether the application enables one to use the invention.

The Office alleged that undue experimentation would be required for one of skill in the art to make and use the claimed polypeptides, citing the Federal Circuit case of *In re Wands,* 8 USPQ2d 1400 (Fed Cir. 1988). The Office observed, "Claim 20 only contains the limitation wherein the fragment is sufficient to produce an antibody which binds . . . ." The Office observed that "this property would need to be confirmed by further testing." However, according to *Wands,* these allegations do not negate patentability. The *Wands* case involved the question of enablement with respect to antibody production, based on the state of the art that existed several years before the present application was filed. In *Wands,* it was unpredictable which individual antibodies would satisfy the claimed invention, but it was acknowledged that the desired antibodies could be made and identified through the exercise of *routine screening.* Screening does not render a specification non-enabling, especially when the screening is routine in nature, such as the screening involved in antibody production and testing. What was routine screening of antibodies at the time of the *Wands* invention certainly was more routine years later, when the present application was filed.

There exists a well-established expectation that peptides can be used to generate an immune response, *i.e.*, to generate specific antibodies. The attached declaration by Dr. Alitalo (and its exhibits) demonstrates that whatever testing is necessary, it does not

constitute undue experimentation. Techniques for producing and testing antibodies were well known in the art and routine by 1992, as were methods of identifying fragments of a given protein that produce antibodies with desired properties. Using the Federal Circuit's approach set forth in the *Wands* case, the proper characterization of the present invention is that *it is predictable from the application* that when fragments of Flt4 are produced as described in the application, a large number of working embodiments will be identified with only routine screening.

Accordingly, the claims are enabled by the application as filed, the rejection is improper, and the rejection should be withdrawn.

VII. THE CLAIMS FIND SUFFICIENT WRITTEN DESCRIPTIVE SUPPORT IN THE SPECIFICATION AS FILED

Beginning on page 8 of the action, the Office rejected claims 19-22, 24, 31 and 33 under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse.

Contrary to the Office's assertions, the claims do specify distinguishing attributes shared by the members of the claimed genus. Members of the claimed genus each comprise Flt4 amino acid sequence taught in Figure 2, the sequence listing (SEQ ID NOS: 2 and 4), and elsewhere in the specification. The Flt4 amino acid sequence differs from the sequence of any prior art protein and, as discussed in greater detail below, serves to distinguish the compounds of the invention from other peptides/polypeptides. The Flt4 sequence (*e.g.*, from SEQ ID NO: 4) define the structure relevant to making Flt4 antibodies, and one skilled in the art can reasonably predict (from amino acid sequence and comparison to prior art sequences) which peptide fragments will be useful for making Flt4-specific antibodies. Thus, one skilled in the art would conclude that the disclosure of the Flt4 sequence and other teachings in the application meant that the inventors were in possession of the claimed invention. Accordingly, the claims find written descriptive support in the application as filed and the rejection should be withdrawn.

VIII. THE CLAIMS ARE NOT ANTICIPATED BY TERMAN

The Office rejected claims 20-21, 24, 31, and 33 as allegedly anticipated by Terman et al. (1991) under 35 U.S.C. § 102(b). Applicants respectfully traverse and, for the

purposes of this response, take Terman et al. (1991) to refer to Terman et al., Oncogene, 6: 1677-1683 (1991) referenced in the specification at pages 38 and 39. The sequence used by the Examiner in the Sequence Comparison A supplied with the action, while sharing some sequence with that in the Terman article, is not identical to the sequence supplied in the Terman article and is also dated (at the earliest) June 1, 1994, which is after the effective filing date claimed in the present application (October 9, 1992).

Claims 20 and 24 (and consequently, claims depending therefrom) recite "the fragment includes sufficient amino acid sequence of SEQ ID NO: 2 or 4 to generate an immune response in a nonhuman mammal to produce antibodies that specifically bind to Flt4." Accordingly, the Flt4 fragments encompassed must contain such sequence and be of such a length so that they produce antibodies that are specific to Flt4. A peptide fragment from VEGFR-2 (including the KDR fragment/variant presented in the figures of the Terman article) would not produce an antibody that specifically binds Flt4. Instead, such a fragment would produce antibodies specific to KDR. Even if a few hypothetical peptides could be made (based on knowledge of KDR and Flt4 sequence) that consist only of common epitopes between KDR and Flt4, such peptides would fall outside the scope of the claims, because the antibodies would not be "specific" to Flt4; they would cross-react with Flt4 and VEGFR-2.[2] A similar argument applies to VEGFR-1 peptides fragments. Accordingly, the sequence presented by the Terman article does not anticipate claims 20, 24, or claims dependent therefrom.

Claim 33 recites peptides comprising SEQ ID NO: 4 fragments that have amino acid sequences defined by cyanogen bromide cleavage sites.[3] The application teaches the Flt4 amino acid sequence (*e.g.*, SEQ ID NOS: 2 and 4) and that fragments may be

[2] Moreover, Terman does not explicitly disclose such hypothetical, short peptides, but rather, discloses a different sequence that falls outside the current claims.

[3] Cyanogen bromide cleaves peptides C-terminal to methionine residues.

generated using cyanogen bromide.[4] *See, e.g.*, the specification at page 32, lines 9-14. None of the claimed fragments share complete identity with the sequences of Flt1 or KDR.

Accordingly, the claims are not anticipated by Terman and the rejection should be withdrawn.

CONCLUSION

Applicants respectfully request prompt consideration of the pending claims. Claims 19-24 and 31-33 are believed to be in condition for allowance in view of the foregoing amendments and remarks.

Applicants invite the Examiner to contact the undersigned attorney if questions arise during examination, or if the Examiner has suggestions for expediting allowance.

Respectfully submitted,

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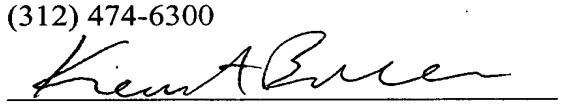
By: 

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[4] Exhibit D of Dr. Alitalo's declaration provides a series of nine amino acid sequences for the "CNBr fragments" recited in claim 33. These sequences are the same as those provided in Exhibit A of Applicants' March 2004 preliminary amendment. Exhibit D also corrects stop/start positions for the last three fragments, which were inadvertently misidentified in Exhibit A of the March 2004 amendment. As a courtesy to the Examiner, Applicants are also providing the sequence information in an email that is being sent to the Examiner concurrently with the filing of this present amendment and response.